Remarks

The Office Action mailed May 22, 2002 has been received and reviewed. Claims 1-4, 9-12, and 21-40 having been amended, claims 5-8 and 13-20 having been canceled without prejudice and claims 41-44 having been added, the pending claims are claims 1-4, 9-12, and 21-44. Support for the amendments to the claims is found throughout the specification and in the claims as originally filed. For example, support for amended claims 1-4, 9-12 and 21-40 is found in original claims 1, 3, and 9-12. Support for the recitation "isolated" is found, for example, at page 10, lines 21-22 and page 15, line 30 - page 16, line 3 of the specification. Reconsideration and withdrawal of the rejections is respectfully requested

Examiner Walicka is thanked for her courtesy in faxing and mailing copies of the Lu et al., Pierson et al., and Valerie et al. references to the Applicant. Copies of these references had been inadvertently omitted in the mailing of the Office Action.

Request for Rejoinder under 37 CFR §1.121

Claims 21-40, directed to methods of use, which were previously withdrawn from examination pursuant an election filed in response to the Restriction Requirement mailed January 9, 2002, are amended herewith to include all the limitations of the examined product claims. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), withdrawal of the restriction requirement as it relates to claims 21-40, and rejoinder and examination of previously withdrawn claims 21-40, as amended herein, is respectfully requested.

The Objection to the Specification

The Examiner objected to the disclosure, stating that page 12, line 5 of the disclosure "contains an embedded hyperlink and/or other form of browser-executable code." MPEP §608 - "Hyperlinks and Other Forms of Browser-Executable Code in the Specification," states "that hyperlinks and other forms of browser-executable code . . . are not [to be] included in a patent application." As explained in the Examiner Note section of MPEP §608, "[e]xamples of a

hyperlink or a browser-executable code are a URL placed between these symbols '<>' and a http:// followed by the URL address." Page 12, line 5 of the specification recites "www.ncbi.nlm.nih.gov/gorf/b12.html." This recitation lacks both the "<>" and the "http://" designations, and thus, does not qualify as a hyperlink or a browser-executable code according to the definition provided in MPEP §608. Thus, it is respectfully submitted that the information presented on page 12 of the specification is in proper format. Withdrawal of this objection to the specification is respectfully requested.

The 35 U.S.C. §101 Rejection

The Examiner rejected claims 1-12 under 35 U.S.C. §101, as directed to non-statutory subject matter. Claims 1, 3, 5 , 7 and 9-12 have been amended to recite an "isolated polypeptide." Withdrawal of this rejection under 35 U.S.C. §101 is respectfully requested.

The 35 U.S.C. §112, First Paragraph, Written Description Rejection

The Examiner rejected claims 1-9 and 11-12 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserted that the claims, drawn to polypeptides having pyrimidine glycosylase activity and 15% identity to SEQ ID NO:41, 42 or 43, "encompass a large genus of pyrimidine glycosylase enzymes from any organism and man made sources." However, as "the specification fails to teach a structure function relationship for the claimed enzymes" and discloses only three species of the claimed genus (SEQ ID NO:41, 42 and 43), the specification "is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus" and "one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed."

This is respectfully traversed. To meet the written description requirement of 35 U.S.C. §112, first paragraph, the application "must convey with reasonable clarity to those skilled in the

art that, as of the filing date sought, he or she was in possession of the invention, i.e., what is now claimed." M.P.E.P. § 2163. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Claim 9 is drawn to an "isolated polypeptide comprising: an amino acid sequence selected form the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43; and a targeting sequence." It is respectfully submitted that the specification provides adequate written description for the three species (SEQ ID NO:41, 42 and 43) of claim 9. This is shown, for example, by the disclosure of the amino acid sequences of SEQ ID NO:41, 42 and 43 in Figure 24. This is also acknowledged by the Examiner, with her statement that the "specification discloses only three species of the claimed genus, SEQ ID NO:41, 42 and 43."

Further, it is respectfully submitted that adequate written description is provided for claims 1-4 and 11-12. Claims 1-4 and 11-12 are drawn to isolated polypeptides that 1) have an amino acid sequence having at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and 2) have pyrimidine glycosylase activity (claims 1-4) or pyrimidine glycosylase /AP lyase activity (claims 11 and 12). Thus, the polypeptides of claims 1-4 and 11-12 are claimed by both a physical characteristic (having an amino acid sequence at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43) and a functional characteristic (having pyrimidine glycosylase or pyrimidine glycosylase /AP lyase activity).

The specification provides detailed information for making polypeptides with the claimed physical characteristics of the polypeptides of claims 1-4 and 11-12. The specification provides the amino acid sequences of SEQ ID NO:41, SEQ ID NO:42 and SEQ ID NO:43 (see, for example, Figure 24). The specification also provides detailed instructions for making polypeptides with an amino acid sequence having at least about 15 % identity with an amino

acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43. See p. 11, line 15 - p. 12, line 16 of the specification. Likewise, the specification provides complete information for making polypeptides with the claimed functional characteristics, having pyrimidine glycosylase or pyrimidine glycosylase /AP lyase activity. See, for example, p.8, lines 14-24; p. 9, line 19 - p. 10, line 26; p. 43, line 24- p. 44, line 22; and p. 52, line 17 - p. 53, line 15 of the specification.

Applicants respectfully submit the present specification conveys with reasonable clarity to those skilled in the art that, as of the filing date, Applicants were in possession of the invention. Applicants respectfully maintain that they have satisfied the written description requirement for claims 1-4, 9 and 11-12. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, are respectfully requested.

The 35 U.S.C. §112, First Paragraph, Enablement Rejection

The Examiner rejected claims 1-8 and 11-12 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner asserted that the specification does not reasonably provide enablement for any pyrimidine glycosylase that is at least 15% identical to SEQ ID NO:41, 42, or 43. The Examiner stated that, as "[n]either the claims nor the specification disclose all pyrimidine glycosylases, ie obtained from any organism or man-made sources . . . to make the claimed invention, one skilled in the art would have to perform undue experimentation." Further, the Examiner asserted that "[w]ithout the further guidance on the part of the Applicants as to the source of the DNA molecules, the experimentation left to those skilled in the relevant art is undue."

This rejection is respectfully traversed. As the Examiner acknowledged, the Wands factors are to be considered in determining whether undue experimentation is required. The Wands factors include (a) the quantity of experimentation necessary, (b) the amount of direction and guidance presented, (c) the presence or absence of working examples, (d) the nature of the

invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claims. (*In re Wands*, 858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)).

Claims 1-4 and 11-12 are drawn to isolated polypeptides that have an amino acid sequence having at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and have pyrimidine glycosylase activity (claims 1-4) or pyrimidine glycosylase /AP lyase activity (claims 11 and 12). The specification provides detailed information for making polypeptides with the claimed physical characteristics of the polypeptides of claims, polypeptides having at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43. See p. 11, line 15 - p. 12, line 16 of the specification. Likewise, the specification provides detailed information for making polypeptides with the claimed functional characteristics, having pyrimidine glycosylase or pyrimidine glycosylase /AP lyase activity. See, for example, p.8, lines 14-24; p. 9, line 19 - p. 10, line 26; p. 43, line 24- p. 44, line 22; and p. 52, line 17 - p. 53, line 15 of the specification. Thus, it is respectfully submitted that the specification presents ample direction and guidance. Additionally, with SEQ ID NO:41, 43 and 43, the specification provides several working examples. As the Examiner has acknowledged, the level of skill in the relevant art is high, as the techniques of "gene cloning, sequencing, manipulations, expressing in host cells, isolating proteins from host cells, measuring enzymatic activity and protein sequencing are well known."

Thus, in order to make the claimed polypeptide, one skilled in the art need only, for example, (a) isolate or synthesize a candidate polypeptide; (b) sequence the candidate polypeptide to determine if the candidate polypeptide has at least 15% identity with the amino acid sequence of SEQ ID NO:41, 42 or 43; and (c) conduct a straightforward enzymatic assay to determine whether the candidate polypeptide has pyrimidine glycosylase or pyrimidine glycosylase /AP lyase activity. None of these steps involves undue experimentation, and all are within the ordinary skill of an art worker in the field.

The Examiner asserted that "routine experimentation in the art does not include cloning, sequencing . . . and measuring enzymatic activity of a large number of polypeptides, from any biologic or man-made source, and selecting those that have pyrimidine glysosylase activity and/or are 15% identical to SEQ ID NO:41, 42 or 43. Without further guidance on the part of Applicants as to the source of the DNA, the experimentation left to those skilled in the relevant art is undue." This statement is respectfully traversed. The Examiner has misinterpreted what qualifies as "undue experimentation." Enablement is not precluded by the necessity for experimentation, such as routine screening. The key word is "undue" not "experimentation." *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). It is well-settled that a considerable amount of experimentation is permissible if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (1982).

It is not undue experimentation that the polypeptides of the claimed invention can be obtained from a wide variety of sources. The use of screening methods to screen large numbers of candidate polypeptides to identify and select particular polypeptides of interest is standard practice, and art workers are highly skilled in the use and evaluation of such screening procedures. What is required is sufficient guidance to identify and select the polypeptides that satisfy the limitations of the claims. It is respectfully submitted that the present specification provides sufficient guidance to one of skill in the art to identifying the claimed polypeptides; polypeptides having at least about 15% identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43 (see p. 11, line 15 - p. 12, line 16 of the specification) and having pyrimidine glycosylase or pyrimidine glycosylase /AP lyase activity (see, for example, p.8, lines 14-24; p. 9, line 19 - p. 10, line 26; p. 43, line 24-p. 44, line 22; and p. 52, line 17 - p. 53, lines 15-16 of the specification). This guidance is sufficient to allow one of skill in the art to identify the claimed polypeptides with only routine experimentation. It does not require undue experimentation to practice the claimed invention commensurate with the scope of the claims. Withdrawal of this rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

The 35 U.S.C. §102 Rejection over Nielsen et al.

The Examiner rejected claims 1 and 2 under 35 U.S.C. §102 as being anticipated by Nielsen et al. (Nucleic Acid Research, 25, 750-755 (1997)). Specifically, the Examiner asserted that Nielsen et al. teaches human uracil-DNA glycosylase, a pyrimidine glycosylase, containing an N-terminal nuclear or mitochondrial targeting sequence, that is the same as that claimed. This rejection is respectfully traversed. Claims 1 and 2 are drawn to an isolated polypeptide, the polypeptide having pyrimidine glycosylase activity, at least about 15% amino acid identity with SEQ ID NO:41, SEQ ID NO:42, or SEQ ID NO:43, and a targeting sequence. To anticipate a claim, the reference must teach each and every element of the claim (see MPEP § 2131). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). It is respectfully submitted that Nielsen et al. does not teach a polypeptide having at least about 15% amino acid identity with SEQ ID NO:41, SEQ ID NO:42, or SEQ ID NO:43. Thus, Nielsen et al. does not teach each and every element of claims 1 and 2, and does not anticipate claims 1 and 2. Withdrawal of this rejection under 35 U.S.C. §102, is respectfully requested.

35 U.S.C. §102 Rejection over Otterlei et al.

The Examiner rejected claims 3 and 4 under 35 U.S.C. §102 as being anticipated by Otterlei et al. (Nucleic Acid Research, 26, 4611-7617 (1998)). Specifically, the Examiner asserted that Otterlei et al. teaches a human uracil-DNA glycosylase, a pyrimidine glycosylase, with an exogenous targeting sequence that is the same as that claimed. This rejection is respectfully traversed. Claims 3 and 5 are drawn to an isolated polypeptide, the polypeptide having pyrimidine glycosylase activity, at least about 15% amino acid identity with SEQ ID NO:41, SEQ ID NO:42, or SEQ ID NO:43, and an exogenous targeting sequence. As discussed above, to anticipate a claim, the reference must teach each and every element of the claim (see MPEP § 2131). It is respectfully submitted that Otterlei et al. does not teach a polypeptide having at least about 15% amino acid identity with SEQ ID NO:41, SEQ ID NO:42, or SEQ ID

NO:43. Thus, Otterlei et al. does not teach each and every element of claims 1 and 2, and does not anticipate the claims. Withdrawal of this rejection under 35 U.S.C. §102, is respectfully requested.

The 35 U.S.C. §103 Rejection

The Examiner rejected claims 9 and 10 under 35 U.S.C. §103 as being unpatentable over any one of Lu et al. (Virology, 206, 339-352 (1995)), Valerie et al. (Nucleic Acid Research, 12, 8085-8096, 1984)), or Piersen et al. (J. Biol. Chem., 270, 23475-23484, (1995)), each in view of Nielsen et al. (Nucleic Acid Research, 25, 750-755 (1997)) and Otterlai et al. (Nucleic Acid Research, 26, 4611-7617 (1998)).

Specifically, the Examiner stated that Lu et al., Valerie et al. and Piersen et al. teach polypeptides having pyrimidine glycosylase/AP lyase activity identical to SEQ ID NO:41, 42 or 43, respectively. The Examiner admitted that Lu et al., Valerie et al. or Piersen et al. do not teach polypeptides containing targeting sequences. However, the Examiner stated that Nielsen et al. teaches a human glycosylase containing a natural targeting sequence and Otterlai et al. teaches a human glycosylase containing an exogenous targeting sequence. The Examiner asserted that it would have been obvious to one of ordinary skill in the art to modify the pyrimidine glycosylase of SEQ ID NO:41, 42, or 43, as taught by Lu et al., Valerie et al. and Piersen et al., by fusing targeting sequences to the enzyme as taught by Nilsen et al. or Otterlei et al., "because the latter references teach that attaching targeting sequences to the instant enzymes would aid in targeting the proteins to selected cellular organs." The Examiner continued by asserting that the "motivation would be to obtain a medicinal product that repairs DNA damage caused by UV light, and to make this product the most efficient by targeting the cellular organelles when DNA is localized, i.e., to cell nucleus and mitochondria," and that the "expectation of success in targeting the enzyme to cell nucleus or mitochondria is 100% because this process is natural in mammalian cells."

This rejection is respectfully traversed. To establish a prima facie case of obviousness there must be some suggestion or motivation, either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. (MPEP § 2143). This teaching or suggestion to make the claimed combination must be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claim 9 is drawn to an isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43 and a targeting sequence and claim 10 is drawn to an isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43; and an exogenous targeting sequence.

Lu et al., Valerie et al. and Piersen et al. teach only the polypeptides comprising SEQ ID NO:41, 42 and 43, respectively. These polypeptides are of viral or bacterial origin and have pyrimidine glycosylase activity. As the Examiner acknowledged, the polypeptides taught by Lu et al., Valerie et al. and Piersen et al. do not comprise targeting sequences. Further, Lu et al., Valerie et al. and Piersen et al. do not teach fusing polypeptides having pyrimidine glycosylase enzymatic activity to additional polypeptide sequences, such as targeting sequences; they do not teach products, such as medicinal products, comprising polypeptides having pyrimidine glycosylase activity; and they do not teach targeting polypeptides to selected cellular regions.

Nilsen et al. teaches a human glycosylase containing a natural targeting sequence. Otterlai et al. teaches the further characterization of this human glycosylase by teaching the preparation of constructs with deletion or point mutations within the endogenous targeting sequence. As the Examiner acknowledged, the polypeptides taught by Nilsen et al. and Otterlai et al. do not comprise SEQ ID NO:41, 42 or 43. Further, Nilsen et al. and Otterlai et al. do not teach removing the endogenous targeting sequence and fusing it to a heterologous polypeptide, they do not teach products, such as medicinal products, comprising polypeptides having pyrimidine glycosylase activity; nor do they teach increasing the efficiency of targeting polypeptides to selected cellular regions by the fusion of a targeting sequence.

It is respectfully submitted that the requisite motivation to combine or modify the teachings of the prior art to produce the claimed invention is not found in the teachings of the

cited references or in any combinations of the cited references. A person of skill in the art would not be motivated by reading Lu et al., Valerie et al. or Piersen et al. to modify the amino acid sequences disclosed by Lu et al., Valerie et al. or Piersen et al. with the addition of a targeting sequence disclosed by Nilsen et al. and Otterlai et al. Likewise, one of skill in the art would not be motivated by reading Nilsen et al. and Otterlai et al. to replace the amino acid sequence of human glycosylase with an amino acid sequence disclosed by Lu et al., Valerie et al. or Piersen et al. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. (MPEP § 2143.01). Applicant further submits that even if the cited documents were combined, there would be no reasonable expectation of success.

Withdrawal of the rejection of claims 9 and 10 under 35 U.S.C. §103 is respectfully requested.

Summary

It is respectfully submitted that the pending claims 1-4, 9-12, and 21-44 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
Board of Regents, The University of Texas System

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

26813

PATENT TRADEMARK OFFICE

August 22, 2002
Date

By: David L. Provence

David L. Provence
Reg. No. 43, 022
Direct Dial (612)305-1005

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EV 152753922 US Date of Deposit: August 22, 2002
The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

By: Sara E. Olson
Name: Sara E. Olson

APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS
INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/864,866
Docket No.: 265.00170101

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted. Additionally, all amendments have been shaded.

In the Claims

For convenience, all pending claims are shown below.

1. (Amended) A**n isolated** polypeptide [**having pyrimidine glycosylase activity, the polypeptide**] comprising:

an amino acid sequence having pyrimidine glycosylase activity, the amino acid sequence having at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43; and

a targeting sequence.

2. (Amended) A composition comprising the [**polynucleotide**] **polypeptide** of claim 1 and a pharmaceutically acceptable carrier.

3. (Amended) [**A**] **An isolated** polypeptide [**having pyrimidine glycosylase activity, the polypeptide**] comprising:

an amino acid sequence having pyrimidine glycosylase activity, the amino acid sequence having at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43; and

an exogenous targeting sequence.

4. (Amended) A composition comprising the [**polynucleotide**] **polypeptide** of claim 3 and a pharmaceutically acceptable carrier.

5. (Cancel)

6. (Cancel)

7. (Cancel)

8. (Cancel)

9. (Amended) A**n isolated** polypeptide comprising:

an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43; and

a targeting sequence.

10. (Amended) A**n isolated** polypeptide comprising:

an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43; and

an exogenous targeting sequence.

11. (Amended) A**n isolated** polypeptide comprising:

an amino acid sequence having pyrimidine glycosylase/AP lyase activity, the amino acid sequence having at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43; and

a targeting sequence.

12. (Amended) A**n isolated** polypeptide comprising:

an amino acid sequence having pyrimidine glycosylase /AP lyase activity, the amino acid sequence having at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43; and

an exogenous targeting sequence.

13. (Cancel)

14. (Cancel)

15. (Cancel)

16. (Cancel)

17. (Cancel)

18. (Cancel)

19. (Cancel)

20. (Cancel)

21. (Amended) A method for increasing the repair rate of damaged bases in a cell, the method comprising introducing to a cell exposed to or at risk of exposure to an agent that damages DNA a composition comprising an amount of [a] **an isolated** polypeptide effective to increase the repair rate of damaged DNA in the cell compared to a cell that does not comprise the polypeptide, wherein the polypeptide [**has pyrimidine glycosylase activity and**] **comprises an amino acid sequence having pyrimidine glycosylase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further** comprises a targeting sequence.

22. (Amended) A method for increasing the repair rate of damaged bases in a cell, the method comprising introducing to a cell exposed to or at risk of exposure to an agent that

damages DNA a composition comprising an amount of [a] **an isolated** polypeptide effective to increase the repair rate of damaged DNA in the cell compared to a cell that does not comprise the polypeptide, wherein the polypeptide [**has pyrimidine glycosylase activity and**] **comprises** an amino acid sequence having pyrimidine glycosylase activity**, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further** comprises an exogenous targeting sequence.

23. (Amended) A method for increasing the repair rate of damaged bases in a cell, the method comprising introducing to a cell exposed to or at risk of exposure to an agent that damages DNA a composition comprising an amount of [a] **an isolated** polypeptide effective to increase the repair rate of damaged DNA in the cell compared to a cell that does not comprise the polypeptide, wherein the polypeptide [**has pyrimidine glycosylase/AP lyase activity and**] **comprises an amino acid sequence having pyrimidine glycosylase/AP lyase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further** comprises a targeting sequence.

24. (Amended) A method for increasing the repair rate of damaged bases in a cell, the method comprising introducing to a cell exposed to or at risk of exposure to an agent that damages DNA a composition comprising an amount of [a] **an isolated** polypeptide effective to increase the repair rate of damaged DNA in the cell compared to a cell that does not comprise the polypeptide, wherein the polypeptide [**has pyrimidine glycosylase/AP lyase activity and**] **comprises an amino acid sequence having pyrimidine glycosylase/AP lyase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further** comprises an exogenous targeting sequence.

25. (Amended) A method for treating mutagenesis in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [**a**] **an isolated** polypeptide**, wherein the polypeptide comprises an amino acid sequence** having pyrimidine glycosylase activity**, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43,** and **wherein the polypeptide further comprises** [**comprising**] an targeting sequence.

26. (Amended) A method for treating mutagenesis in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [**a**] **an isolated** polypeptide**, wherein the polypeptide comprises an amino acid sequence** having pyrimidine glycosylase activity**, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43**, and **wherein the polypeptide further comprises** [**comprising**] an exogenous targeting sequence.

27. (Amended) A method for treating mutagenesis in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [**a**] **an isolated** polypeptide**, wherein the polypeptide comprises an amino acid sequence** having pyrimidine glycosylase/AP lyase activity**, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43,** and **wherein the polypeptide further comprises** [**comprising**] a targeting sequence.

28. (Amended) A method for treating mutagenesis in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [**a**] **an isolated** polypeptide**, wherein the polypeptide comprises an amino acid sequence** having pyrimidine glycosylase/AP lyase activity**,**

wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] an exogenous targeting sequence.

29. (Amended) A method for treating immunosuppression in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] a targeting sequence.

30. (Amended) A method for treating immunosuppression in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] an exogenous targeting sequence.

31. (Amended) A method for treating immunosuppression in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase/AP lyase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] a targeting sequence.

32. (Amended) A method for treating immunosuppression in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase/AP lyase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] an exogenous targeting sequence.

33. (Amended) A method for treating tumor formation in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] a targeting sequence.

34. (Amended) A method for treating tumor formation in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] an exogenous targeting sequence.

35. (Amended) A method for treating tumor formation in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase activity/AP lyase

activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] a targeting sequence.

36. (Amended) A method for treating tumor formation in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase/AP lyase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] an exogenous targeting sequence.

37. (Amended) A method for treating apoptotic cell formation in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] a targeting sequence.

38. (Amended) A method for treating apoptotic cell formation in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] an exogenous targeting sequence.

39. (Amended) A method for treating apoptotic cell formation in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase/AP lyase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] a targeting sequence.

40. (Amended) A method for treating apoptotic cell formation in a subject, the method comprising introducing to a subject exposed to or at risk of exposure to an agent that damages DNA a composition comprising an effective amount of [a] an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence having pyrimidine glycosylase/AP lyase activity, wherein the amino acid sequence has at least about 15 % identity with an amino acid sequence selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, and SEQ ID NO:43, and wherein the polypeptide further comprises [comprising] an exogenous targeting sequence.

41. (New) **A composition comprising the polypeptide of claim 9 and a pharmaceutically acceptable carrier.**

42. (New) **A composition comprising the polypeptide of claim 10 and a pharmaceutically acceptable carrier.**

43. (New) **A composition comprising the polypeptide of claim 11 and a pharmaceutically acceptable carrier.**

44. (New) **A composition comprising the polypeptide of claim 12 and a pharmaceutically acceptable carrier.**